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A fractional order impedance individualised model of nociceptor stimulation ⋆

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Abstract: This paper introduces a mathematical model and methodology for detecting and analysing nociceptor stimulation effects by means of non-invasive evaluation of the skin impedance in the hand palm. The derivation of the model is based on multi-scale physiological stages during perception of pain in awake individuals and contains elements of fractional calculus. The result is a lumped fractional order impedance model, to be used in a personalised way, i.e. per individual and not per population distribution data. A measurement device and a protocol have been determined in collaboration with Ghent University Hospital pain specialists. The experiments support our claim that changes occur in skin impedance during stimulation, i.e. when perceived as pain in one awake healthy volunteer. Following this proof of concept study, the model enables simulation of how nociceptor stimulation enters the systemic process of pain, for further analysis and development within the regulatory loops of pain management practices.

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Keywords: nociceptor pathway, chronic pain, analgesia, bioimpedance, fractional order impedance models, non-invasive measurement, mathematical model

1. INTRODUCTION

For patients undergoing general anesthesia or staying in the intensive care unit (ICU), there was until very recently (two-three years) no objective or analytical tool ready at hand to evaluate the level of pain they are experiencing (Haddad et al., 2007). It was even reported that 35% to 55% of nurses tend to underrate patient's pain (Puntillo et al., 2002), mainly due to the difficulty of non-awake patient analgesic level assessment or psycho-emotional aspects in awake patients. Moreover, in (Puntillo et al., 1997) has been reported that 64% of the patients did not receive any medications before or during painful procedures.

In the last two-to-three years, some devices have come on the market for pain assessment. MEDSTORM (`www.medstorm.com`) measures the conductivity of skin as a constant value calculated over time windows, and is only applicable in anesthetized (non-awake) patients, and measures not only pain, but also alertness and movement. MEDASENSE (`www.medasense.com`) is based on a surrogate of multi-dimensional analysis and is not available for purchase in Europe at this time. ALGISCAN (`via IDMed France`) is a scanner based on pupillometry and measures dillatation of the eye pupil as a reaction to pain stimuli, requiring a fixed setting on patient's eye and eyelids open during the fully anesthetised intervention.

Effective management of analgesia in the ICU units (i.e. a mixture of awake and non-awake patients) requires an assessment of the needs of the patient, subjective and/or objective measurement of the key variables (such as pain, agitation, and level of consciousness). It is important to admit that patient needs can differ depending on clinical circumstances, and that for any given patient therapeutic targets are likely to change over time, mainly due to drug trapping (Copot et al., 2017).

The present paper reports on the preliminary results obtained with the proposed method and protocol for detecting nociceptor stimulation. Mathematical models are evaluated on experimental data successfully. The models represent two types of characterisation of dynamic systems, namely classical pole-zero transfer function models and emerging models from fractional calculus, namely fractional order impedance model (FOIM) in non-rational form of the Laplace operator (Ionescu et al., 2017). Some details on the latter type of model parameter are given in Appendix.

The paper is summarized as follows: the next section introduces the methodology and models used for characterizing the skin impedance for nociceptor stimulation evaluation. The third section summarizes the results and a conclusion section ends this paper with some further use of the acquired information.

2. PROPOSED METHODOLOGY AND MODELS

2.1 Measurement Protocol

Three study cases have been analysed:

- case 1 - perform two consecutive measurement protocols to investigate the repeatability and existence of pain memory. Sensors are placed on the right hand

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and the nociceptor stimulation is applied at the same location (i.e. same hand);
- case 2 - perform only one measurement as in case 1, but on a consecutive day (same hour during the day) - to test day-to-day variability in the data;
- case 3 - perform one measurement to investigate whether the sensor placement influences the measured result, i.e. the electrodes are placed on the right hand palm, while the nociceptor stimulation is applied on the left hand.

All these cases have been investigated on one awake, healthy, volunteer, age 35, height 171cm, weight 83 kg, female. In each case, the protocol summarized in Table 1 has been applied.

Table 1. The time intervals and actions within the 10 minute measurement protocol. The P/NP denote the acronym used in figures to indicate the case.

Time Interval (min)	Nociceptor stimulation
0-2	Absent (NP)
2-3	Present (P)
3-6	Absent (NP)
6-7	Present (P)
7-10	Absent (NP)

2.2 Methodology

There is an established relation between nociceptor pathway and dynamics of potassium channels, also referred to as the *sodium-potassium pump*, for signaling between the intra- and extra-cellular fluid in the biological tissue (Schuttler and Schwilden, 2008). An increase in potassium concentration in the extracellular fluid is observed to vary between 0.1 and 10.0 mmol/L and depends on stimulation frequency, intensity, and duration of the nociceptor stimulus (McMahon et al., 2013). In vitro validation studies have been performed to verify the use of the proposed models for detecting changes in the concentration of these cations in controlled environment solutions (Copot et al., 2016). Changes in the electro-chemical composition of the extracellular fluid may be assessed by means of bio-electrical-impedance, i.e. via the skin (Yang et al., 2015). The working principle is based on sending an excitation electrical signal to the skin (i.e. sinusoid, multisine, etc), while measuring its response as voltage and current changes.

For this purpose, a prototype device has been developed in our laboratory, ANSPEC-PRO, depicted in figure 1.

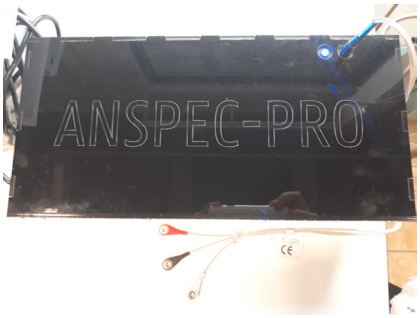

Fig. 1. The ANSPEC-PRO prototype for non-invasive measurement of bio-electrical skin impedance.

The measurement flowchart can be summarized as follows:

- optimize a multisine signal with 29 components in the frequency interval 100-1500 Hz, with step interval of 50Hz
- send this signal and acquire the measured signals at sampling frequency of 15 KHz
- the multisine signal is send with an amplitude of 0.2mA, still a factor 5 below the maximum allowed by clinical standards (Fish and Geddes, 2009).
- use a 3M 3-point electrode sensor in the hand-palm CE-marked (according to MDD93/42/EEC)
- measure current and voltage via a National Instruments (Texas, USA) device (cRIO9074 with NI9201- and NI9263-slots)
- store the signals online in computer for further processing.

The computer used for the study is a laptop with the operating system Windows 7 Enterprise 64-bit and a INTEL(R) Core(TM) i7-6600U CPU@2.80GHz processor. A graphical user interface allows monitoring of signal quality.

A reliable measurement requires a three-point electrodes: two current-carrying electrodes and one pick-up electrode (we used 3M standard electrodes commercially available). The latter is measuring the voltage without carrying any currents, hence, no polarization occurs. All electrodes were placed on the palm side of the hand. A calibration of the measurements was performed apriori by measuring for 10 minutes without nociceptor stimulus applied and without removing the electrodes.

2.3 Mathematical Models

Non-Parametric Models The measured signals are filtered for noise prior to apply non-parametric identification methods (Pintelon and Schoukens, 2001). Given the input is of sinusoidal type ($A\sin(\omega t)$), the impedance is a frequency dependent complex variable evaluated as:

$$Z(j\omega) = \frac{S_{XX}(j\omega)}{S_{XY}(j\omega)} \tag{1}$$

where $S_{XX}(j\omega)$ denotes the auto-correlation spectrum of the signal, $S_{XY}(j\omega)$ denotes the cross-correlation spectra between the input-output signals, $\omega = 2\pi f$ is the angular frequency in rad/s, with f the frequency in Hz, and $j = \sqrt{-1}$. Classical periodogram filtering technique has been applied with no overlapping interval, with windowing function Blackman implemented in Matlab environment (Pintelon and Schoukens, 2001). The impedance is then evaluated every minute from online data streaming and plotted against frequency. This is then a frequency response either in complex form (Real and Imaginary Parts), either in Bode plot form (Magnitude and Phase).

Zero-Pole Transfer Function Model From the frequency response determined at the previous step, one is able to identify a parametric model in the form of a rational function in the complex variable $s = \sigma + j\omega$, that is:

$$H(s) = \frac{b_m s^m + b_m s^{m-1} + \cdots + b_1 s + b_0}{a_n s^n + a_{n-1} s^{n-1} + \cdots + a_1 s + a_0} \tag{2}$$

with m and n the coefficient number and b and a polynomials. Often, these polynomials are factorized in zero-pole form:

$$H(s) = K\frac{(s-z_1)(s-z_2)\dots(s-z_{m-1})(s-z_m)}{(s-p_1)(s-p_2)\dots(s-p_{n-1})(s-p_n)} \quad (3)$$

Fractional Order Impedance Model Originating our prior work on modelling biological tissue with fractional order impedance models (FOIMs), the following extension is proposed.

The physiological pathway of pain can be described to four main processes (Schuttler and Schwilden, 2008):

- transduction — when a stimulus is applied to the skin, the nociceptors located there trigger action potentials by converting the physical energy from a noxious thermal, mechanical or chemical stimulus into electrochemical energy,
- transmission — the signals are subsequently transmitted in the form of action potentials (similar to pulse trains) via nerve fibers from the site of transduction (periphery) to the dorsal root ganglion, which then activates the interneuron,
- perception — the appreciation of signals arriving in specified areas in the cerebral cortex as pain, and
- modulation — descending inhibitor and facilitator input from the brainstem that influences (modulates) nociceptive transmission from the spinal cord.

The stimulus effect to nociception reception is essentially considered an ultra-capacitor, which is represented by a non-rational form of transfer function model in $(j\omega)^n$, with n any real number (Gabriel et al., 1996). Specifically, skin -electrode interface, stratum corneum and ionic pathways can be modelled as elements in an electrical network. Various models describe this interface using constant or current-depending resistive-capacitive equivalent circuits (Vargas Luna et al., 2015). Using fraction expansion theory, a lumped FOIM can be obtained as a fractional order integral (Ionescu et al., 2011). Similarly, *transmission* in signalling pathways occurs via neuronal activity, already modelled with FOIMs from resistance - inductance equivalent electrical network elements (Ionescu, 2012), expressed by a fractional order derivative.

The perception model based on exponential and power law combined functions seems to be a good candidate for capturing essential electrical activity modulated in brain (Bogacz, 2017). Plasticity in synaptic variance is introduced in a layer-based sensory area in cortex by reverse node engineering modelling (Tononi, 2004). In the case of pain perception, the combined effect can be obtained by using the Mittag-Leffler function, which is well-known to capture hybrid exponential and power-law behaviour in biological tissues (Ionescu et al., 2017).

Diffusion of perception sensory activity in brain using Mittag Leffler function in time domain corresponds to a non-integer order derivative easily expressed in frequency domain (Zhou et al., 2010). Layered activity can be represented by ladder networks with serial connection of RC-cells. To account for plasticity, the RC cells are not identical, instead they behave as a memristor with unbalanced dynamics. For instance, it is expected that the first pain perception is more intense than the second, given the latency of the delayed pain stimulus (i.e. sharp first increase followed by slowly decaying tail).

Assuming the brain-cortex area as a porous tissue whose porosity varies (i.e intra- and extra- cellular space tissue with different densities), one can model the changes in viscosity as a function of this porous density. It has been shown that fractional order derivatives are natural solutions to anomalous diffusion equations (Nicholson, 2001). The net advantage of using the Mittag-Lefler function is that it allows introducing memory formalism (Trujillo, 2006), therefore taking into account the tissue rheology. The mixed area in brain tissue will introduce a dynamic viscosity and thus a dynamic perception of nociceptor induced pain (Lundstrom et al., 2008). Finally, the perception and modulation activity can be characterized yet again by a FOIM as differ-integral (depending on the sign of the non-rational order) (Lundstrom et al., 2008; Ionescu, 2012).

Combining all the above information to fit the multi-scale nociceptor pathway, one obtains the complete lumped FOIM model:

$$Z_{FOIM}(s) = R + \frac{TD}{s_1^\alpha} + \frac{TS}{s_2^\alpha} + Ps_3^\alpha \quad (4)$$

where $\alpha_1, \alpha_2, \alpha_3 \in (-1, 0) \cup (0, 1)$ and TD-denotes transduction, TS denotes transmission and P denotes perception. A calibration factor has been added, a gain R. We claim that not all terms in this model are necessary at all times, as some of the physiological processes may be impaired in some applications (e.g. analgesia will put zero the effect of the perception term in P) (Crosby et al., 2015). The units are arbitrary, as the model is defined as a difference to the initial state of the patient - due to the use of fractional derivatives - and not as absolute values. This enables patient specificity since no generic model is assumed to be valid and thus broadcasts a new light upon the interpretation of such models.

2.4 Statistical Analysis

One way `anova` has been used to compare among the group of values. The function `anova1` has been used in Matlab which returns box plots of the observations in data y, by group. Confidence intervals have been calculated at 95%, and significant differences defined for $p - values < 0.05$. The function `ttest` in Matlab has been used. A multiple comparison test has also been performed, using `multcompare` command in Matlab. Two medians are significantly different at the 5% significance level if their intervals do not overlap.

3. RESULTS AND DISCUSSION

3.1 Frequency Response Complex Impedance

The frequency response of the complex impedance calculated using (1) is depicted in Figure 2 for one individual test. In this figure one may observe the various values of impedance in presence/absence of nociceptor stimulation. This validates our hypothesis that changes in the extracellular fluid electro-chemical composition is measurable non-invasively via skin.

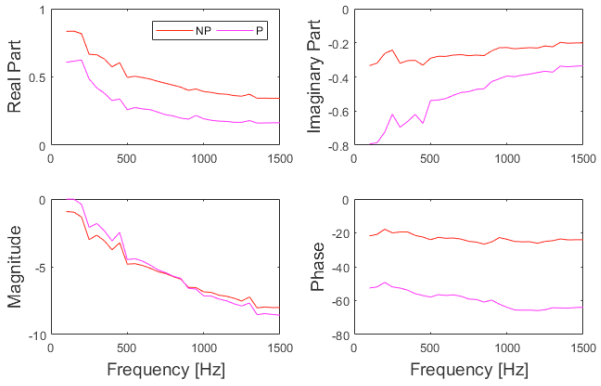

Fig. 2. Normalized impedance as a function of frequency by means of its real and imaginary parts, calculated per interval of absent(NP)/present(P) nociceptor stimulation.

The self-evaluation based on the Wong-Baker scale (see figure 3) was around 1-2.

Fig. 3. Wong-Baker scale of pain perception.

3.2 Transfer Function Model

For the same individual, for the pain interval, the fitting of the transfer function model from (3) onto the frequency response complex impedance data is depicted in figure 4. The fitting was obtained using nonlinear least squares identification with the Matlab command `lsqnonlin`, with steepest gradient descent, in an iterative manner. Iteration was performed as to avoid local minimum and the number of iterations between the identified results varied between #2-#4 in all data. The iteration was stopped when the model parameters changed less that 5%.

3.3 FOIM Model

For the same individual, for the pain P1 interval, the fitting of the FOIM model from (4) onto the frequency response complex impedance data is depicted in figure 5. The fitting was obtained in the same manner as for the model (3).

3.4 Variability within Individual

To analyse the variability within individual among the three investigated situations, the frequency response obtained using (1) has been used. For this analysis, the absolute values of the frequency response complex impedance per excited frequency point has been used.

There was no significant difference within individual per protocol in either nociceptor stimulation case P1 ($p < 0.311$) or P2 ($p < 0.28$). See figure 6.

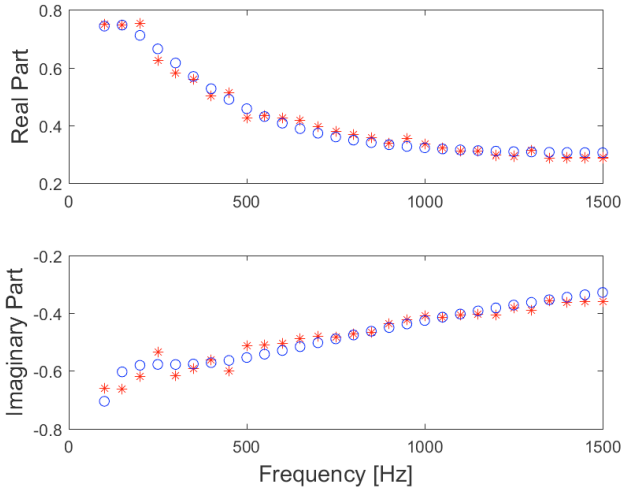

Fig. 4. Identified transfer function model for the data P1 depicted in figure 2.

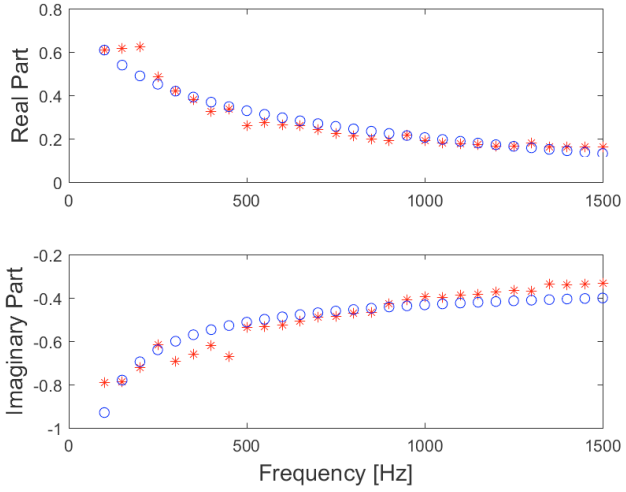

Fig. 5. Identified FOIM model for the data P1 depicted in figure 2.

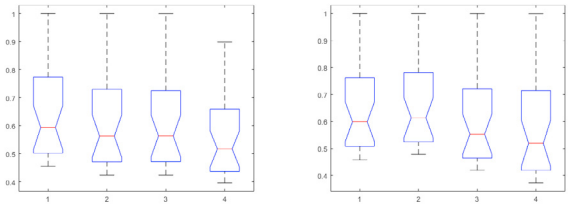

Fig. 6. Anova analysis of absolute values of frequency response complex impedance in one individual per protocol. Group 1 and Group 2 belong to case study #1, namely the two consecutive measurements. Group 3 and Group 4 denote the case study #2 and #3, respectively. Figure on left for P1 stimulation time interval, figure on right for P2 stimulation time interval.

3.5 Discussion

It is important to understand that the method and models developed here are uniquely defined for each individual.

In other words, the reporting of the model values is not relevant here because the data is expressed with respect to the initial moment of measurement, whereas the state of the patient is taken as a reference. Hence, all values reported are in fact calibrated for that reference value of impedance and thus each individual has its own initial state values.

The use of FOIMs is now justified by the data in some sense that indeed, tissue memory exists and it is a feature naturally explained with properties of mathematical models from fractional calculus. The detailed description of properties of FOIMS has been given in numerous other reports, hence it is omitted here (Podlubny, 2002).

The relevance of the data is nevertheless important, for it brings a method, device and mathematical models to provide an indication of change in bioelectrical impedance measured via skin electrodes correlated with absence/presence of nociceptor stimulation. This is then a first step towards developing a full objective measurement setup and algorithm for quantifying related pain levels.

Our proposed tools are in the same line of thought as those presented in (Shieh et al., 2007, 2006). An intelligent analysis system based on fuzzy logic models was successfully tested in post-operative patients, whereas patient-controlled analgesia (Morphine based) was titrated from the determined index. With respect to their work, our work differs in that it delivers a mathematical framework related to the actual tissue dynamics (i.e. memory, dielectric) properties and thus justifies the use of FOIMs.

The present study is limited in the number of individuals measured. The missing correlation to clinical practice indexes such as Wong-Baker faces scale or other numerical scores, should be performed on a larger population in order to extract a mathematical relationship between model parameters and clinical levels of pain. Although the method is personalised, i.e. the values are calibrated to the initial state of the individual/patient, an analysis of the influence of BMI on the accuracy of the estimators should be performed. The authors do not claim the values given here are reference values. They are specific for the individuals included in this study and calibrated for each individual in part.

4. CONCLUSION

In this work we provide a methodology and mathematical framework to model the nociceptor stimulation effect in healthy aware and awake individuals. The method used is bio-electrical impedance by means of non-invasive skin electrode measurement. The models proposed are physiologically based without direct correlation to the physiologicval quantities, i.e they are calibrated for initial state of the individual. This implies a personalised assessment of nociceptor stimulation effect perceived as pain, hence unique parameterization of model values.

5. APPENDIX

The fractional calculus is a generalization of the differential and integral operators into one fundamental operator D_t^n (n the order of the operation) which is known as *fractional calculus*. Several definitions of this operator have been proposed (see, e.g. (Podlubny, 2002)). All of them generalize the standard differential–integral operator in two main groups: (a) they become the standard differential–integral operator of any order when n is an integer; (b) the Laplace transform of the operator D_t^n is s^n (provided zero initial conditions), and hence the frequency characteristic of this operator is $(j\omega)^n$. The Fourier transform can be obtained by replacing s by $j\omega$ in the Laplace transform and the equivalent frequency-domain expressions are:

$$(j\omega)^{\pm n} = \omega^{\pm n}\left(\cos\frac{n\pi}{2} \pm j\sin\frac{n\pi}{2}\right) \tag{5}$$

Thus, the modulus and the argument of the FO terms are given by:

$$Modulus(dB) = 20\log\left|(j\omega)^{\mp n}\right| = \mp 20n\log|\omega| \tag{6}$$

$$Phase(rad) = arg\left((j\omega)^{\mp n}\right) = \mp n\frac{\pi}{2} \tag{7}$$

resulting in:

- a Nyquist contour of a line with a slope $\mp n\frac{\pi}{2}$, anticlockwise rotation of the modulus in the complex plain around the origin according to variation of the FO value n;
- Magnitude (dB *vs* log-frequency): straight line with a slope of $\mp 20n$ passing through 0dB for $\omega = 1$;
- Phase (rad vs log-frequency): horizontal line, thus independent with frequency, with value $\mp n\frac{\pi}{2}$.

The respective sketches can be seen in figure 7.

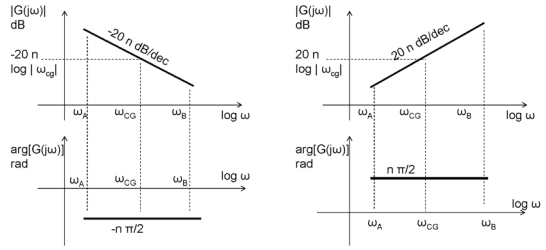

Fig. 7. Sketch representation of the FO integral and derivator operators in frequency domain, by means of the Bode plots (Magnitude, Phase)

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